# PATENT COOPERATION TREATY



From the
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) | |
| Applicant's or agent's file reference<br>see form PCT/ISA/220 | **FOR FURTHER ACTION**<br>See paragraph 2 below |
| International application No.<br>PCT/US2005/006108 | International filing date *(day/month/year)*<br>24.02.2005 |
| Priority date *(day/month/year)*<br>24.02.2004 | |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K48/00, A61K38/17, A61P35/00 | |
| Applicant<br>INTROGEN THERAPEUTICS, INC. | |

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/006108

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. II Priority**

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-30 with respect to industrial applicablity

because:

☒ the said international application, or the said claims Nos. 1-30 with respect to industrial applicablity relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 6, 7, 11, 13-28 |
| | No: | Claims | 1-5, 8-10, 12, 29, 30 |
| Inventive step (IS) | Yes: | Claims | None |
| | No: | Claims | 1-30 |
| Industrial applicability (IA) | Yes: | Claims | - |
| | No: | Claims | - |

2. Citations and explanations

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. Claims 1-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). However, an international search report based on the alleged effects of the products / compositions in question has been established for such claims since their subject matter can readily and in a straightforward manner be understood in terms of these effects. Accordingly, an opinion on novelty and inventive step of the subject matter of these claims is also now given in as far as relating to the alleged effects of the products / compositions in question (see PCT Rule 33.3(b) and 66.1(a)).

2. Following from the above, claim 1 has been interpreted as being directed to essentially the effects of a combination of a **nucleic acid encoding p53 and a source of radiotherapy or chemotherapy** in treating a recurrent cancer in a **patient in whom a prior surgical, radiotherapeutic or chemotherapeutic treatment** for the cancer has been performed. A similar interpretation mutatis mutandis has been given to the subject matter of claims 2-30 dependent on claim 1.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: J. Clin. Oncol. 18, 2000, 609-622

D2: Cancer Gene Therapy, 9, 2000, 567-572

D3: BIOSIS PREV199799548911

D4: BIOSIS PREV199799596956

D5: Clinical Cancer Research, 4, 1998, 835-846

D6: Cancer Chemother Pharmacol., 1999, 44, 143-151

D7: Proc. Am. Assoc. Can. Res. Ann. Meet., vol. 40, 1999, 596

Attention is drawn in particular to all passages of these documents as indicated on the International Search Report, unless stated otherwise.

**D1**: Patients with non-small cell lung cancer, some with prior platinum based therapy, cisplatin at day 1, Ad-53 at day four. Evidence of clinical activity
**D2**: Ad-p53 delivered in combination with cisplatin or carboplatin/paclitaxel, effects on various cancers, eg ovarian; patients had previously received platinum treatment
**D3**: JSQ-3 is a squamous cell carcinoma of head and neck, radiation resistant cell line, having a mutant p53 gene. JSQ-3 based mouse xenograft tumours as in vivo tumour model, enhanced tumour regression with radiotherapy when performed in combination with Ad-p53 vector delivery
**D4**: Introduction of p53 gene into squamous cell carcinoma of head and neck via Ad vector, xenografted in mice, presence of p53 sensitises tumour to radiation (ie enhanced cell killing)
**D5**: Ad-p53 gene transfer studies in vitro and in vivo. In SHNCC model (SCC-15 cell based tumours), combination therapy with 5 FU and vector achieved greater antitumour activity then entities used alone (unclear as to order of use)
**D6**: SCID mice with various tumour models, eg ovarian. Delivery of Ad-p53 and paclitaxel, effect synergistic in comparison with entities delivered alone
**D7**: Lung carcinoma mouse xenograft having mutated p53 gene, delivery thereto of wild type p53 via Adenovirus vector, restoration of apoptosis mediated chemosensitivity. Paper also proposes use of ligand-liposome based p53 gene delivery to overcome limitations of Ad vectors in p53 gene delivery, indicating use of the same sensitises inter alia head and neck tumour cells in vivo to chemotherapeutic agents. Likely use in treating primary tumours, and also metastases and recurrent tumours.

1. Novelty (Art. 33(2) PCT and Inventive Step (Art. 33(3) PCT)

An opinion on novelty and inventive step is now given for the subject matter of the claims interpreted in the way indicated under Item III.
In light of the prior art as analysed hereinabove, the subject matter of claim 1 lacks novelty over D1, D2. Over the other prior art claim 1 lacks inventive step: assuming the difference between claim 1 and their subject matter residing in the nature of the patient to be treated (claim 1, **one in which a prior** surgical, radiotherapeutic or chemotherapeutic treatment for the cancer has been performed), inter alia since the skilled person would immediately

choose such patients as candidates to be further treated by a therapeutic regimen, realising that such patients had been unsuccessfully treated by the therapeutic regimen previously carried out, the skilled person would then arrive at the subject matter of claim 1 as a matter of routine and without the exercising of inventive skill. It is in addition to be noted that should novelty of the subject matter under consideration possibly be acknowledged by virtue of any technical feature relating to the order in which p53 nucleic acid and chemotherapy / radiotherapy is administered (ie vector followed by chemotherapy / radiotherapy), this subject matter would in any case lack inventive step since the benefits of choosing such an order of administration (namely sensitisation to in particular the chemotherapeutic agent by previously delivered p53 gene) is known from for example D7.

Over the prior art cited, the subject matter of claims 2-30 in addition either lacks novelty, or if novel, lacks inventive step since the claimed subject matter would be derived by the skilled person starting from the prior art cited as a matter of routine in the field concerned.

2. For the assessment of the present claims 1-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.